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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,616	07/28/2003	Hiroyuki Osada	P23771	3320

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,616	OSADA ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 26 September 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) 1-7 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10/28/2003.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 are pending.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 26 Sep 2006 is acknowledged. The traversal is on the ground(s) that the searches for Inventions I and II should significantly overlap because the claims in Group I and II both relate to the same Plk mutant nucleic acid sequence. This is not found persuasive because Group I is drawn to a method of detecting protein and Group II is drawn to a method of detecting nucleic acid. Nucleic acid and the protein present structurally and functionally distinct inventions. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter, restriction for examination purposes as indicated is proper. Upon review and reconsideration claims 8-11 have been placed into Group II.

Claims 1-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 8-14 are under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: obtaining samples for the detections (See material and method section of Knecht et al, Cancer Res 1999, 59:2794-2797) and determination steps to achieve the purpose stated in the preamble. It needs to define sample source and relating steps linking the detection of the mutant genes and/or the mutant proteins to diagnosing a malignant tumor or detecting an abnormal cell.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Claims 8-14 are drawn to method for diagnosing a malignant tumor cell comprising detecting the presence of a mutant Plk nucleotide sequence.

The specification discloses that 4 out of 9 cancer cell lines had mutations in the C-terminus of Plk and that these mutations correlate with expression levels of PLk protein (page 13, 1st and 2nd paragraphs). However, the specification fails to teach any correlation between the presence of the two mutant Plks, Plk (S487G, P509S) and Plk (N496S, R512W), and diagnosing a malignant tumor or detecting an abnormal cell. The specification does not teach that low expression of Plk, low affinity of Plk for Hsp90 or instability of Plk protein due to low affinity for Hsp90 leads to malignant tumor. The specification at page 13, line 1and 2 says "low expression levels of...may contribute to tumorigensis in human cancers." However, the specification does not teach low level expression of Plk is correlated with tumorigensis.

Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although

the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders and associated markers such as CIN and HLA alleles and HPV type. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

Unlike checkpoint genes, which decreased level of protein expression leads to tumorigensis in human cancers (page 13, lines 1-2), McInnes et al (Curr Topics Med Chem, 2005, 5:181-197) teaches that high expression of Plk is associated with many

different human cancers (page 183, 2nd column, 3rd paragraph to page 184, 1st column, 1st paragraph) . The most urgent issues that the specification has not taught in order to use the instant invention for the purpose stated in the preamble in claims 8-14 are 1) any human primary malignant tumor or any human primary abnormal cell has the mutant Plks, Plk (S487G, P509S), and Plk (N496S, R512W); note that all data in the instant application were obtained using established cell lines, 2) normal tissue-type, sex, age-matched cells do not have the mutants, 3) detection of mutant Plk (S487G, P509S) and/or mutant Plk (N496S, R512W) lead to the purpose stated in the preamble of claims 3-14 by verification of presence of malignant tumor by one or more reliable independent methods for detecting cancers. Therefore the mutants cannot be used as a tumor marker either as genes or proteins. Considering the teachings of McInnes that the increased, not decreased, expression of a Plk protein is associated with cancer, limited teachings of the specification, and no working examples of diagnosing malignant tumor by detecting the mutant Plk or detecting low expression of Plk due to decreased affinity for Hsp90, it is concluded that undue experimentation is necessary for the mutant Plk to be used to detect malignant tumors or abnormal cells, or to be used as a tumor marker either as genes or proteins.

Summary

No claims allowed

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson, PhD
Patent Examiner
571-272-6539

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PRIMARY EXAMINER